Massive transfusion in trauma

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Purpose of review
The purpose of this review is to provide an overview of currently recommended treatment approaches for traumatic hemorrhage shock, with a special focus on massive transfusion.

Recent findings
Severe trauma patients require massive transfusion, but consensual international definitions for traumatic hemorrhage shock and massive transfusion are missing. Current literature defines a massive transfusion as transfusion of a minimum of 3–4 packed red blood cells within 1 h. Using standard laboratory and/or viscoelastic tests, earliest diagnosis and treatment should focus on trauma-induced coagulopathy and substitution of substantiated deficiencies.

Summary
To initiate therapy immediately massive transfusion protocols are helpful focusing on early hemorrhage control using hemostatic dressing and tourniquets, correction of metabolic derangements to decrease coagulopathy and substitution according to viscoelastic assays and blood gases analysis with tranexamic acid, fibrinogen concentrate, red blood cells, plasma and platelets are recommended. Alternatively, the use of whole blood is possible. If needed, further support using prothrombin complex, factor XIII or desmopressin is suggested.

Keywords
blood component, hemorrhage, massive transfusion, traumatic injury, viscoelastic hemostatic assay

INTRODUCTION

Trauma accounts for 15% of perioperative massive transfusion (MT) [1▪▪,2▪▪] and, following traumatic brain injury (TBI), hemorrhage remains the leading cause of death, especially in individuals aged ≤46 years [3▪]. Hemorrhagic shock (HS) is present in up to 40%; nevertheless, in 12–34% of trauma and hemorrhage, deaths are preventable [4▪]. Some 6 percentage of trauma patients appear to be at risk of requiring MT [1▪▪,5▪]. This review will focus on recent developments in MT in trauma.

METHODS

We performed a selective review of the literature using structured search strategies in a timeframe from 2003 to 2023.

DEFINITION

MT is a treatment for massive hemorrhage. The European guideline on management of severe perioperative bleeding defines 'severe' as beyond 20% of total blood volume [TBV) [6▪▪]. Both class III [30–40% loss of TBV, systolic blood pressure (SBP) <90 mmHg, heart rate ([HR) ≥120/min and thready] and class IV (>40% TBV) of the Advanced Trauma Life Support's four classes of hemorrhage should be considered as 'massive' [1▪▪,7▪]. Blood loss (BL) of 1.5 l, which equals approximately 30% of an adult's TBV, causes consistent hypotension [4▪]. A consensual international definition of traumatic HS is necessary but missing: the most used parameters are Shock Index (SI; ≥0.9), SBP, base excess (BE; ≤−5 mmol/l), lactate (>3 mmol/l), and number of transfused packed red blood cells (pRBC) [8▪▪]. Using SI, defined as HR divided by SBP, a systematic review including a total of 670 728 trauma patients showed values correlated with the degree of shock and impaired tissue perfusion, SI >1 is indicative of

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SHOUT
SHARE
IT

KEY POINTS

- Continuous measurement of temperature and serial measurement of blood gases.
- Initially ratio-driven, as soon as possible concentrate based individualized goal-directed substitution.
- For HS: permissive hypotension; 15 mg/kg tranexamic acid; fibrinogen aiming at 2.2–2.5 g/l; PCC 25 IU/kg; factor XIII (if <60%) 20 IU/kg.
- Consider cell salvage.

suspect HS, but should not be used as a sole parameter [9▪▪]. The British 2022 Guideline on major hemorrhage abstained from a definition, but emphasized the patient's clinical status (e.g., HR > 110/min and/or SBP < 90 mmHg). An increased risk of massive hemorrhage is to be expected in adults with SBP <70 mmHg, adults with HR >110/min and SBP <90 mmHg (the most recurrent definition for HS [8▪▪]), penetrating injury or major fractures, and fluid in body cavities likely to be blood [1▪▪]. Most definitions use the transfused number of pRBC. Multiple definitions for MT are published, varying greatly in cut-offs for volume transfused and time frame [2▪▪]. MT's historical definition dates to the Vietnam War and entails ≥10RBC/24 h [5▪]. As most exsanguinating deaths occur within 2 h of bleeding onset [4▪], using 24 h will imply a 'survivorship bias' [2▪▪,8▪▪]. MT is an outcome measure encompassing both patients' wellbeing and resource utilization [2▪▪]. Table 1 lists possible definitions for MT.

Table 1. Definitions of MT

Traditional definition	≥10 pRBC/24 h ≥20 pRBC/24 h (ultra massive)
Modern definition	≥10 pRBC/6 h ≥20 pRBC/4 h (ultra massive) ≥4pRBC/1 h Loss of ≥50% TBV/3 h Loss of TBV in 24 h
Substantial bleeding	≥1 pRBC within 2 h and ≥5 pRBC or bleeding-related death within 4 h
Resuscitation intensity (RI)	Number of units infused within 30 min of arrival 1 unit = 1 l crystalline solution, 0.5 l colloid, 1 pRBC, 1 plasma, or 6 platelets (~ 1 pooled or apheresis unit)
Critical administration threshold (CAT) positive	≥3 pRBC CAT24 h: in any 1 h within 24 h of arrival CAT1 h: within 1 h CAT4 h: in any 1 h within 4 h

Compared to ≥10RBC/24 h, 'CAT positive' has the best sensitivity, but 'RI positive' has better specificity as well as better positive and negative predictive values [1▪▪]. RI is the only definition not exclusively using pRBC [2▪▪]. pRBC, packed red blood cells, TBV, total blood volume.

PATHOPHYSIOLOGY

Impaired microcirculation leads to cellular hypoxia causing endothelial damage. Loss of the endothelial glycocalyx is emerging as a unifying mechanism linking the endotheliopathy of trauma with microvascular inflammation, barrier leakage, coagulopathy, and organ injury. Endothelial injury and glycocalyx shedding, causing sympathoadrenal activation, occurring 5–8 min after injury and persisting for 24 h, are determined by the severity of HS. Both hypoxia and hypoperfusion cause release of tissue-plasminogen activator (t-PA) from endothelial Weibel-Palade bodies. Rather than the injury itself, downstream effects of the injury are postulated to result in glycocalyx degradation causing hyperfibrinolysis and increased mortality. Microcirculatory derangements can persist despite adequate macrocirculation corrected by vasopressors or transfusion. This ischemia-induced hyperfibrinolysis is a major contributor to trauma-induced coagulopathy (TIC) and of special importance in low-flow states [10▪,11▪,12▪▪,13▪].

DIAGNOSTICS

Coagulopathy might visually be diagnosed by non-surgical, diffuse bleeding from mucosa, serosa, wounds as well as punction sites of intravascular catheters. Basic analysis requires early and repetitive measurements of blood gases (BGA), blood typing, and conventional coagulation tests (CCT), that is, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, platelet count [6▪▪,14▪▪,15▪▪].

Early and serial BGAs and temperature are the easiest, cheapest, and fastest monitoring and should be done every 20–30 min or every 4 pRBC in patients being actively resuscitated [1▪▪,15▪▪,16▪▪]. Increasing lactate and negative BE are sensitive tests to monitor the extent of bleeding and tissue hypoperfusion, essential for diagnosing coagulopathy [15▪▪–17▪▪], and indicative even prehospitally [18▪]. The context of hypothermia, acidosis and coagulopathy is emphasized by the terms "*bloody vicious cycle*" [19], "*lethal triad*" [20], and "*triad of death*" [21]. A recent focus on transfusion- and trauma-induced hypocalcemia as a fourth inducing coagulopathy aimed at an ionized calcium of

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>0.9 mmol/l [6▪▪] and introduced the term *"death diamond"* [22]. Figure 1 lists these parameters.

It is well recognized that CCT may not provide real-time assessment of a patient's hemostatic status, a more rapid generation of results will improve patient care [1▪▪]. Additionally, PT and aPTT were not designed to monitor coagulation deficiencies during hemorrhage. Use of point-of-care devices in MT is effective for both, diagnostics and therapy: viscoelastic hemostatic assays (VHA) and platelet *function* analyzers. VHA are highly specific for hyperfibrinolysis, more sensitive in the early detection of coagulopathy than CCT, might improve survival [6▪▪,23▪] and are useful to guide individualized goal-directed coagulation therapy [6▪▪,15▪▪–17▪▪]. Regardless of BL, VHA's high negative predictive value indicates when there is no need for supplementation thereby reducing unnecessary transfusion! The German 2023 guideline uses a grade of recommendation A for VHA and B for platelet function [14▪▪]; the European guideline states, that diagnostic cut-offs for pathologic platelet dysfunction after traumatic injury have not been established [17▪▪].

THERAPY

The main approach must be to prevent MT [4▪,5▪,6▪▪]. Therefore, a stepwise concept of direct pressure, hemostatic-impregnated compression dressings and tourniquets should be used initially to control bleeding [14▪▪,15▪▪].

With signs of ongoing bleeding, hemodynamic instability or clinical gestalt, therapy should rapidly be started [24▪].

Synthetic colloids should be avoided [16▪▪]. Contemporary strategies minimize balanced crystalloid use ("restrictive volume replacement strategy") [16▪▪,25▪].

MASSIVE TRANSFUSION PROTOCOL

Local establishment of site-specific, standardized, multidisciplinary massive transfusion protocols (MTP) with predefined cut-offs, components, and ratios form the basis of standardizing transfusion [6▪▪,15▪▪,16▪▪,26▪▪].

WARMING DEVICES

Exclusively warmed fluids and the use of warming devices are essential for fluid therapy [15▪▪,26▪▪].

DAMAGE CONTROL RESUSCITATION

Damage control resuscitation (DCR) focuses on the early use of whole blood (WB) or blood product ratios, early hemorrhage control, permissive hypotension to promote hemostasis, and correction of ongoing metabolic derangements, followed by rapid definitive hemorrhage control [24▪].

RED BLOOD CELLS

The decision to transfuse is always an individual one [27▪]. RBC are used to maintain hemoglobin (Hb) at a level high enough to support adequate oxygen delivery to the tissues. Transfusion is usually required when 30–40% of TBV is lost (~1500 ml in a 70 kg male). Loss of more than 40% TBV

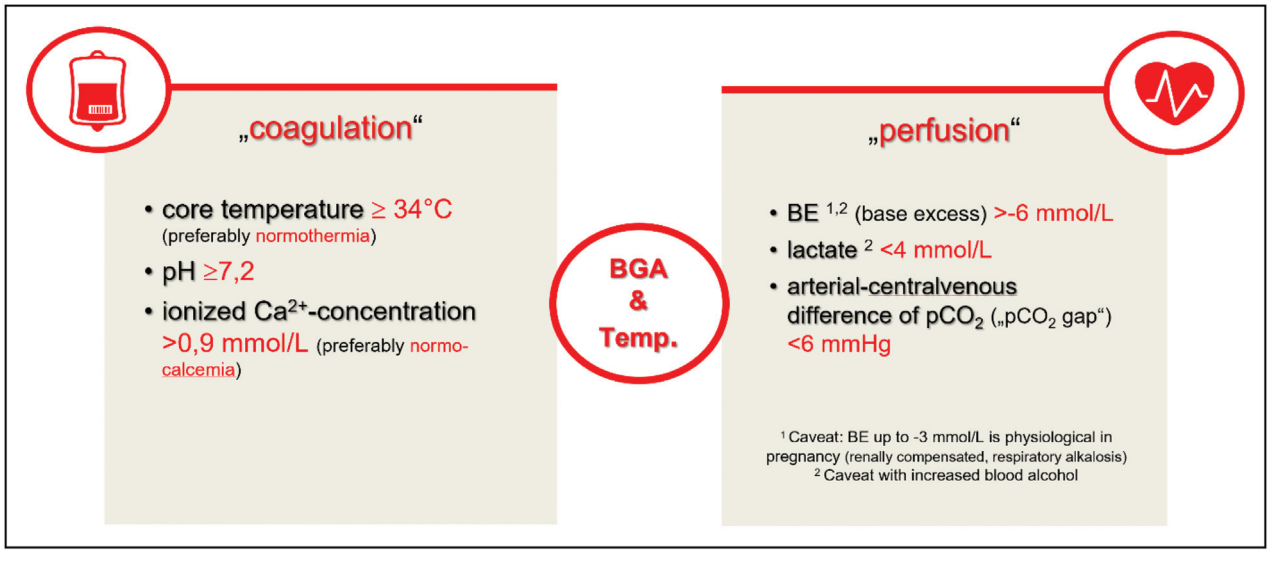
„coagulation"
• core temperature ≥ 34°C (preferably normothermia)
• pH ≥7,2
• ionized Ca2+-concentration >0,9 mmol/L (preferably normocalcemia)
BGA & Temp.
„perfusion"
• BE 1,2 (base excess) >-6 mmol/L
• lactate 2 <4 mmol/L
• arterial-centralvenous difference of pCO2 („pCO2 gap") <6 mmHg
1 Caveat: BE up to -3 mmol/L is physiological in pregnancy (renally compensated, respiratory alkalosis)
2 Caveat with increased blood alcohol

FIGURE 1. Preconditions for functional hemostasis. Treatment targets are given for resuscitation of coagulation and perfusion (modified with a CC-BY-NC-license by Karger).

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(1500–2000 ml) is life threatening and requires immediate transfusion [16▪▪,26▪▪]. A restrictive transfusion threshold of 70–90 g/l (4.3–5.6 mmol/l) was proven to be, at least, noninferior for trauma [28]. Especially in MT, Hb concentration may remain falsely elevated despite significant BL due to inadequate fluid resuscitation. After bleeding control, there is no indication to aim at physiological Hb-levels [26▪▪].

Blood type O, the most common blood type, has lower von Willebrand factor (vWF) and FVIII levels (25–35% lower than non-O blood types); this might be associated with increased bleeding, hyperfibrinolysis, and MT post injury [29].

RBC transfusion should be ABO-identically. Emergency transfusion of un-crossed blood group O is only indicated for vital risk [27▪]. The risk of D-alloimmunization following RhD-positive transfusion seems to be smaller than previously thought [30].

PLASMA

Most plasma consists of either fresh frozen, single-donor plasma (FFP) or pooled plasma from a certain number of donors, for example, solvent/detergent (SD-) treated plasma [31▪▪]. Single-donor plasma contains a variable activity of individual coagulation factors (especially FI and FVIII). FFP is standardized on a FVIII-activity of 70% following thawing. Pathogen-reduction or virus-inactivation by different chemical additives causes additional reduction of specific factors.

FFP should be group-identical to the patient. Group A plasma is now also available for untyped patients demonstrating noninferiority to AB-plasma, the impact of plasma ABO-incompatibility on clinical outcomes is insignificant [25▪]. Being a superior isometric buffer compared to crystalloids, plasma is an ideal volume expander in the intravascular space, has a homeostatic effect on endothelial function and innate immune system activation [25▪,32]. FFP-based resuscitation improves intestinal perfusion immediately following resuscitation, which correlates with improved tissue oxygenation and decreased tissue CO_2-levels [33]. A clinical and significant increase of coagulation factor activities can be achieved by large volumes of plasma only (>30 ml/kg) [31▪▪]. Therefore, the main indication of plasma might be MT [27▪].

PLATELET CONCENTRATES

Due to a lack of controlled trials, an evidence-based statement on platelet cut-offs in different clinical settings is not possible. Based on expert opinion, most guidelines recommend platelet concentrate (PC) for MT if platelet count is <75–100 G/L or a loss of 1.5× TBV [15▪▪,16▪▪,26▪▪,27▪]. Platelet count and platelet function do not necessarily correlate [27▪]. Both quantitative and qualitative platelet damages are more marked when tissue injury is severe, transfusion is large, and hypoperfusion is intense and prolonged. Variations of platelet count within 'normal ranges' might reflect trauma severity and coagulopathy; early platelet transfusion despite normal platelet count might be beneficial [34▪]. Beside PC, the clot's firmness can be increased by desmopressin and/or blocking of fibrinolysis by tranexamic acid (TXA) [6▪▪,26▪▪,27▪].

RATIO

Ratio describes the unit ratios of RBC to FFP to PC. Of note, the order of the components is not standardized. Additionally, different formulations of PC might cause a mix-up of these numbers: One apheresis unit is equivalent to 5-6 whole blood (WB)-derived units. The pooled units available in Australia, Canada and Europe have lower numbers of platelets equivalent to 4–5 single donors. Using pathogen-reduction will cause significant reduction in platelet recovery [1▪▪].

The PROPPR-trial remains the only prospective RCT to find reduced mortality by a 1 : 1:1 ratio; but only for 3 h-mortality, not for 24 h or 30d [35]. This was only achieved when components were available within 8 min of calling the blood bank and artificial colloid fluid use was markedly restricted [36]. A post hoc analysis using Bayesian hierarchical models indicated "strong" to "decisive" supporting evidence in favor of balanced transfusions [37]. Almost all international guidelines recommend this ratio as initial therapy in MT: RBC and plasma initially in a 1 : 1 ratio (not less than 2 : 1) [16▪▪,17▪▪,26▪▪]; RBC:FFP:PC in a 1 : 1:1 (using US PC) [25▪] or 4 : 4:1 ratio (using Australian or German pooled or apheresis PC) [14▪▪,15▪▪], respectively; and a high PC:RBC ratio [17▪▪]. Using the Trauma Quality Improvement Program database, for patients receiving >10 pRBC, increasing RBC:PC and RBC:FFP ratios were consistently associated with increased odds of 4h-mortality [38▪].

In MT, a 'hybrid approach' shall be used: beginning with 'ratio-driven', resuscitation measures shall as soon as possible be continued using an individualized goal-directed strategy, guided by VHA and/or CCT [6▪▪,14▪▪–17▪▪,26▪▪,27▪].

WHOLE BLOOD

The manufacturing process of separating donated blood into single components necessitates the

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addition of ~25% of each bag's volume in additives, preservatives, and stabilizers. Therefore, 1RBC + 1FFP + 1PC will not have the same coagulation activity as the same volume of WB. Recent prospective trials of WB in the civilian setting found increased survival: A prospective observational cohort study of 1377 trauma patients requiring un-crossmatched products found a fourfold increased survival and 60% reduction in overall transfusions [39▪▪]. A 14-center, prospective observational study showed 1623 WB patients to be 9% less likely to experience bleeding complications and 48% less likely to die [40▪]. A prospective, multicenter, observational cohort study of 7 trauma centers with 1051 patients noted in patients with an elevated prehospital probability of mortality a 48% lower risk of 4h-mortality and a 30% lower risk of 28d-mortality [41▪]. A meta-analysis of 20 studies up to January 2023 confirmed lower early and 24h-mortality in WB groups [42▪▪]. A recent meta-analysis showed transfusion with WB + components is associated with lower 24-h mortality vs. component alone and transfusion with WB is associated with a lower volume of RBC transfused at both 6 and 24 h [43▪]. On average, these results were reached with 2 units of WB combined with components. In the USA, low titer type O whole blood (LTOWB), a FDA cleared WB product, is increasingly used for massively bleeding civilians [24▪].

TRANEXAMIC ACID

As hypoxia and hypoperfusion are common in HS and MT and main triggers of hyperfibrinolysis, the early use of TXA is indicated; the administration of TXA shall not await results from VHA [6▪▪,17▪▪]. The recommended dose is 15 mg/kg or 1 g for an adult. Routine administration of a second dose might not be indicated, only in case of persistent or recurrent hyperfibrinolysis [44▪].

COAGULATION FACTOR CONCENTRATES

In the early treatment phase of uncontrolled massive bleeding, a MT with a high ratio (≥1 : 1) of plasma to RBCs is suggested; but, as soon as possible, a concentrate based individualized targeted controlled coagulation management is recommended [6▪▪].

FIBRINOGEN

Hypofibrinogenemia is common in MT. Trauma patients undergoing MT with decreased admission fibrinogen (<2 g/l) demonstrate increased mortality [23▪]. Fibrinogen's physiological concentration of 2.5 g/L is associated with enhanced endothelial barrier integrity [45]. FFP is impractical for increasing fibrinogen levels >1.5 g/l, and supplementation in the form of cryoprecipitate or fibrinogen concentrate (FC) should be chosen [6▪▪,16▪▪,17▪▪,26▪▪,27▪]. Compared to FC, cryoprecipitate appears considerably less predictable for bleeding management due to wide variation in pro- and anticoagulation factors, the presence of PMPs, and the potential to elevate VWF and FVIII to prothrombotic levels [46]. The German guideline recommends FC for life-threatening bleeding and/or HS [14▪▪]. Substitution is indicated, if plasma concentration is <1.5–2 g/l [6▪▪,16▪▪,17▪▪,26▪▪,27▪,47] and should aim at 2.2–2.5 g/l [14▪▪,48,49] or respective VHA-results. An initial dose might be 3–6 g in an adult [15▪▪,16▪▪,26▪▪] or 30–60 mg/kg [14▪▪,16▪▪]. A postulated risk for thromboembolism following FC was never substantiated, probably because of a negative feedback-mechanism of FI as an acute-phase-protein.

PROTHROMBIN COMPLEX CONCENTRATES

Initially, thrombin generation is not impaired in trauma; however, it is substantially depressed by increasing shock with hypoperfusion [50]. Stimulation of thrombin generation might be induced by 4-factor prothrombin complex concentrates (PCC). In the massively bleeding patient with coagulopathy, the administration of an initial bolus of 25 IU/kg is recommended, in those with a high risk for thromboembolic complications an initial half-dose bolus (12.5 IU/kg) should be considered [51]. In a meta-analysis and compared with FFP only, PCC + FFP demonstrated better survival rate, favorable clinical recovery and no elevation of thromboembolism events [52]. Among 2238 adults treated for reversal of warfarin-associated bleeding, receipt of ~25 IU/kg 4F-PCC was not associated with an excess risk of thromboembolic events at 45 days compared with plasma therapy [53▪]. However, in 324 trauma patients with a median injury severity score (ISS) of 36 (26–50) receiving ≥1 pRBC and 25 IU/kg of PCC, thromboembolic events were more common (35% vs. 24%) [54▪]. In this PROCOAG-trial, 40% of patients received ≥3 RBC within the first hour, a median of 6 (4–10) RBC and had a trend towards better survival (+2% for 24 h and 28 days); the endpoint was confounded by survival bias and the product used may differ in efficacy from other PCC [24▪,55]. The German guideline recommends PCC for life-threatening bleeding and/or HS [14▪▪] and only, if fibrinogen is adequate [6▪▪,14▪▪,17▪▪]. Following PCC,

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a thromboembolic rate of 4–11% is recorded and a thorough benefit-risk assessment recommended [27▪,56].

FACTOR XIII

Supported by calcium, FXIII is responsible for covalent fibrin stabilization. With increased BL and hyperfibrinolysis, an acquired FXIII-deficiency is not a rare event [6▪▪,27▪]. FXIII should be monitored in bleeding patients and, in case of functional deficiency, supplemented [17▪▪]. The use of FXIII concentrate with 20 IU/kg at a FXIII level <60% is recommended in some guidelines [14▪▪,17▪▪], albeit this cut-off is still in discussion [6▪▪].

DESMOPRESSIN

In acquired von Willebrand syndrome, that is, platelet function impaired by hypothermia, acidemia, some diseases (valvular, myeloproliferative), extracorporeal assist devices, or drugs (ASS, COX1-inhibitors, ...), weak evidence indicates application of desmopressin (0.3 mg/kg as short infusion) [6▪▪,16▪▪,27▪].

CELL SALVAGE

For every BL >10% TBV, the use of intraoperative cell salvage shall be considered. A more liberal indication for re-transfusion of salvaged blood (compared to RBC) is justified by reduced risks [27▪]. If surgery for malignancy is still a contraindication remains debatable [57].

PERMISSIVE HYPOTENSION

The latest meta-analysis showed significant in-hospital and 30-day survival benefit by permissive hypotension; yet the optimal blood pressure for the individual patient remains vague [58,59]. This is shown by different targets in different guidelines: mean arterial pressure (MAP) 65 mmHg [14▪▪] vs. 50–60 mmHg [16▪▪,17▪▪] or, for traumatic brain injury (TBI), ~85 mmHg [14▪▪] vs. ≥80 mmHg [17▪▪]. The currently available data should be interpreted with caution [17▪▪]. The extent and treatment of HS must be monitored by serial measurement of lactate and BE [14▪▪]. Of note, permissive hypotension should be a temporary measure until the cause of bleeding has been controlled [16▪▪]. If the strategy of restricted volume replacement and permissive hypotension fails to achieve the target blood pressure, transient noradrenaline and/or vasopressin is recommended to maintain tissue perfusion [16▪▪,17▪▪,60].

PEDIATRIC TRAUMATIC HEMORRHAGIC SHOCK

There is little high-quality evidence available to guide specific aspects of hemorrhage control and specific resuscitation practices in this population. In children unlike adults, blood pressure alone is an insensitive indicator of hemorrhagic shock. DCR's principles are largely the same in pediatric and adult patients [61▪]. Recently, the recommendations of a consensus conference were published suggesting comparable but weight-adapted options [62▪▪]. Blood products should be prioritized over crystalloid for pre and in-hospital resuscitation.

MISCELLANEOUS

Morbidity and mortality rates increase as transfusion requirements increase [2▪▪]; yet, there is a debate whether the absolute transfusion volume or the transfusion rate (i.e., >7 units/h at 24 h) provides better discriminatory power for mortality [3▪]. Based on high transfusion volumes alone, futility of resuscitation should not be declared in MT [63]; constantly reevaluating the need for ongoing transfusion is recommended [3▪]. However, during a time of urgent blood bank shortage, a combination of the recently proposed evidence-based STOP-criteria [64] and certain VHA results [65] might be helpful in this evaluation.

Following MT (≥5 RBC within 4 h) about 7% of the patients form new alloantibodies; an independent association with new alloantibody formation was found for transfusion of D-positive RBC to D-negative patients and, to a lesser extent, D-positive PC to D-negative patients, and ≥11RBC in 24 h [66].

PROPHYLAXIS OF THROMBOSIS

Within 24 h following stop of bleeding, start and type of thrombosis prophylaxis should be determined [6▪▪,27▪].

CONCLUSION

HS and MT remain challenging tasks for our multidisciplinary teams. The availability of standardized MTP with predefined cut-offs is essential for being prepared. Serial laboratory measurements are essential and VHA very helpful. The ratio-driven therapy should soon be followed by a goal-directed one.

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Conflicts of interest

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B.H.: lecture fees from CSL Behring.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Hess J. Massive blood transfusion. [www.UpToDate.com]. Wolters Kluwer; ■■ 2023. Available at: https://www.uptodate.com/contents/massive-blood-transfusion [Accessed 29 May 2023].
Regularly updated, peer-reviewed summary of current conceptions on MT.
2. Lin VS, Sun E, Yau S, *et al.* Definitions of massive transfusion in adults with ■■ critical bleeding: a systematic review. Crit Care 2023; 27:265.
First systematic review aiming to identify all MT definitions used in randomized controlled trials to date to inform the development of consensus definitions for MT.
3. Kim JS, Casem CF, Baral E, *et al.* Narrative review: is there a transfusion cutoff ■ value after which nonsurvivability is inevitable in trauma patients receiving ultramassive transfusion? Anesth Analg 2023; 137:354–364.
Analysis of existing literature examining the effects of MT on outcomes including survival in adult trauma patients and to determine whether there is a threshold transfusion limit after which mortality is inevitable.
4. Bonanno FG. Management of hemorrhagic shock: physiology approach, ■ timing and strategies. J Clin Med 2022; 12:260.
Comprehensive review on MT's pathophysiology and resulting options.
5. Gauss T, Moyer JD, Bouzat P. Massive transfusion in trauma: an evolving ■ paradigm. Minerva Anestesiol 2022; 88:184–191.
Opinion paper exposing the evolution and challenging the classic paradigm and historic definition of MT.
6. Kietaibl S, Ahmed A, Afshari A, *et al.* Management of severe peri-operative ■■ bleeding: guidelines from the European Society of Anaesthesiology and Intensive Care: second update 2022. Eur J Anaesthesiol 2023; 40:226–304.
2023 update of the European evidence-based guideline on management of severe peri-operative bleeding.
7. Colwell C. Initial management of moderate to severe hemorrhage in the adult ■ trauma patient. [www.UpToDate.com]. Wolters Kluwer; 2023. Available at: https://www.uptodate.com/contents/initial-management-of-moderate-to-severe-hemorrhage-in-the-adult-trauma-patient [Accessed 29 May 2023]. Regularly updated, peer-reviewed summary of current conceptions on traumatic hemorrhage.
8. James A, Abback PS, Pasquier P, *et al.* The conundrum of the definition of ■■ haemorrhagic shock: a pragmatic exploration based on a scoping review, experts' survey and a cohort analysis. Eur J Trauma Emerg Surg 2022; 48:4639–4649.
Study aiming to explore existing definitions of traumatic hemorrhagic shock and to illustrate the consequences of applying five of these definitions to a trauma registry.
9. Carsetti A, Antolini R, Casarotta E, *et al.* Shock index as predictor of massive ■■ transfusion and mortality in patients with trauma: a systematic review and meta-analysis. Crit Care 2023; 27:85.
Study assessing the accuracy of shock index to predict the need for MT in adult patients with trauma.
10. Bunch CM, Chang E, Moore EE, *et al.* SHock-INduced Endotheliopathy ■ (SHINE): a mechanistic justification for viscoelastography-guided resuscitation of traumatic and nontraumatic shock. Front Physiol 2023; 14:1094845.
Review of endothelial physiology with emphasis on glycocalyx function suggesting the use of VHA for diagnosis and treatment of traumatic HS.
11. Cusack R, Leone M, Rodriguez AH, Martin-Loeches I. Endothelial damage ■ and the microcirculation in critical illness. Biomedicines 2022; 10:3150.
Discussion on the influence of modulated microcirculation in critical illness.
12. Anand T, Reyes AA, Sjoquist MC, *et al.* Resuscitating the endothelial ■■ glycocalyx in trauma and hemorrhagic shock. Ann Surg Open 2023; 4:e298.
Review on the influence of different resuscitation possibilities on the glycocalyx.
13. Cardenas JC, Dong JF, Kozar RA. Injury-induced endotheliopathy: What you ■ need to know. J Trauma Acute Care Surg 2023; 95:454–463.
Current review presenting a synopsis of endothelial cell function in physiological and pathological conditions.
14. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachge- ■■ sellschaften e.V. AWMF-Leitlinie 187-023: S3-Leitlinie Polytrauma /Schwerverletzten-Behandlung. 2023. Available at: https://register.awmf.org/assets/guidelines/187-023l_S3_Polytrauma-Schwerverletzten-Behandlung_2023-02.pdf [Accessed 14 February 2023].
2023 update of the German evidence-based guideline on polytraumatized patients.
15. National Blood Authority Australia. Patient blood management guideline for ■■ adults with critical bleeding. Canberra ACT 2601: National Blood Authority Australia; 2023. Available at: https://www.blood.gov.au/pbm-critical-bleeding [Accessed 17 August 2023].
2023 Australian evidence-based PBM guideline on critical bleeding.
16. Llau JV, Aldecoa C, Guasch E, *et al.* Multidisciplinary consensus document on ■■ the management of massive haemorrhage. First update 2023 (document HEMOMAS-II). Med Intensiva (Engl Ed) 2023; 47:454–467.
2023 update of the Spanish multidisciplinary consensus document on the management of massive hemorrhage.
17. Rossaint R, Afshari A, Bouillon B, *et al.* The European guideline on manage- ■■ ment of major bleeding and coagulopathy following trauma: sixth edition. Crit Care 2023; 27:80.
2023 update of the European evidence-based guideline on polytraumatized patients.
18. Gaessler H, Helm M, Kulla M, *et al.* Prehospital predictors of the need for ■ transfusion in patients with major trauma. Eur J Trauma Emerg Surg 2023; 49:803–812.
Prospective, single-center observational study showing prehospital lactate and base excess being indicative for early transfusion.
19. Kashuk JL, Moore EE, Millikan JS, Moore JB. Major abdominal vascular trauma—a unified approach. J Trauma 1982; 22:672–679.
20. Moore EE, Thomas G. Orr memorial lecture. Staged laparotomy for the hypothermia, acidosis, and coagulopathy syndrome. Am J Surg 1996; 172:405–410.
21. Mikhail J. The trauma triad of death: hypothermia, acidosis, and coagulopathy. AACN Clin Issues 1999; 10:85–94.
22. Ditzel RM Jr, Anderson JL, Eisenhart WJ, *et al.* A review of transfusion- and trauma-induced hypocalcemia: Is it time to change the lethal triad to the lethal diamond? J Trauma Acute Care Surg 2020; 88:434–439.
23. Parker MJ, Crowder EW, Miles MVP, *et al.* Hypofibrinogenemic massive ■ transfusion trauma patients experience worse outcomes. Am Surg 2023; 89:3423–3428.
Prospective study on the effect of admission fibrinogen level and the use of cryoprecipitate on outcomes in trauma patients undergoing MT.
24. Lammers DT, Holcomb JB. Damage control resuscitation in adult trauma ■ patients: what you need to know. J Trauma Acute Care Surg 2023; 95:464–471.
Current review on modern DCR concepts for adult bleeding patients.
25. Beiriger J, Silver D, Lu L, Brown JB. Transfusion management in trauma: what ■ is current best practice? Curr Surg Rep 2023; 11:43–54.
Current review on transfusion management in trauma.
26. Stanworth SJ, Dowling K, Curry N, *et al.* Haematological management of ■■ major haemorrhage: a British Society for Haematology Guideline. Br J Haematol 2022; 198:654–667.
2022 update on the British evidence-based guideline on major hemorrhage.
27. Bundesärztekammer (German Medical Association). Cross-sectional guide- ■ lines for therapy with blood components and plasma derivatives – amended edition 2020. 2020. Available at: https://www.bundesaerztekammer.de/themen/medizin-und-ethik/wissenschaftlicher-beirat/stellungnahmen-richtlinien-jahresberichte/haemotherapie-transfusionsmedizin/querschnitts-leitlinien-baek-zur-therapie-mit-blutkomponenten-und-plasmaderivaten-gesamtnovelle-2020 [Accessed 21 June 2021].
2020 update of the German evidence-based regulatory recommendations on therapy with blood components and plasma derivatives.
28. Hayakawa M, Tagami T, Kudo D, *et al.* The Restrictive Red Blood Cell Transfusion Strategy for Critically Injured Patients (RESTRIC) trial: a cluster-randomized, crossover, noninferiority multicenter trial of restrictive transfusion in trauma. J Intensive Care 2023; 11:34.
29. DeBot M, Eitel AP, Moore EE, *et al.* Blood type O is a risk factor for hyperfibrinolysis and massive transfusion after severe injury. Shock 2022; 58:492–497.
30. Yazer MH, Panko G, Holcomb JB, *et al.* Not as 'D'eadly as once thought – the risk of D-alloimmunization and hemolytic disease of the fetus and newborn following RhD-positive transfusion in trauma. Hematology 2023; 28: 2161215.
31. von Heymann C, Lier H, Rosenthal C, Kaufner L. Indications for the use of ■■ therapeutic plasma in adult patients. Transfus Med Hemother 2023; 50:107–115.
Current discussion on perioperative use of plasma based on the German hemotherapy guideline's updated recommendations.
32. Tucker H, Brohi K, Tan J, *et al.* Association of red blood cells and plasma transfusion versus red blood cell transfusion only with survival for treatment of major traumatic hemorrhage in prehospital setting in England: a multicenter study. Crit Care 2023; 27:25.
33. Schucht JE, Harbrecht BG, Bond LM, *et al.* Plasma resuscitation improves and restores intestinal microcirculatory physiology following haemorrhagic shock. Vox Sang 2023; 118:863–872.
34. Hamada SR, Garrigue D, Nougue H, *et al.* Impact of platelet transfusion on ■ outcomes in trauma patients. Crit Care 2022; 26:49.
Observational study carried out on a French multicenter prospective trauma registry on the impact of early platelet transfusion on 24 h all-cause mortality and on platelet count at admission and its relationship with trauma severity and outcome.

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35. Holcomb JB, Tilley BC, Baraniuk S, *et al.* Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015; 313:471–482.
36. Hess JR, Holcomb JB. Resuscitating PROPPRly. Transfusion 2015; 55:1362–1364.
37. Lammers D, Rokayak O, Uhlich R, *et al.* Balanced resuscitation and earlier mortality end points: bayesian post hoc analysis of the PROPPR trial. Trauma Surg Acute Care Open 2023; 8:e001091.
38. ▪ Dorken-Gallastegi A, Renne AM, Bokenkamp M, *et al.* Balanced blood component resuscitation in trauma: does it matter equally at different transfusion volumes? Surgery 2023; 173:1281–1288.

Data of the American College of Surgeons Trauma Quality Improvement Program database for patients receiving ≥6 RBC, ≥1 PC, and ≥1 FFP within 4 h on the association between balanced blood component transfusion and 4 h-mortality.

39. ▪▪ Brill JB, Tang B, Hatton G, *et al.* Impact of incorporating whole blood into hemorrhagic shock resuscitation: analysis of 1377 consecutive trauma patients receiving emergency-release uncrossmatched blood products. J Am Coll Surg 2022; 234:408–418.

Prospective observational cohort study on the survival benefit of WB across a diverse population of bleeding trauma patients.

40. ▪ Hazelton JP, Ssentongo AE, Oh JS, *et al.* Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. Ann Surg 2022; 276:579–588.

14-center, prospective observational study on the use of WB versus blood component therapy alone causing decreased mortality.

41. ▪ Sperry JL, Cotton BA, Luther JF, *et al.* Whole blood resuscitation and association with survival in injured patients with an elevated probability of mortality. J Am Coll Surg 2023; 237:206–219.

Prospective, multicenter, observational cohort study on the safety and efficacy of LTOWB resuscitation relative to blood component resuscitation.

42. ▪▪ van der Horst RA, Rijnhout TWH, Noorman F, *et al.* Whole blood transfusion in the treatment of acute hemorrhage, a systematic review and meta-analysis. J Trauma Acute Care Surg 2023; 95:256–266.

2023 meta-analysis on the effect of WB ± components as compared to component alone on survival in trauma patients with acute hemorrhage.

43. ▪ Ngatuvai M, Zagales I, Sauder M, *et al.* Outcomes of transfusion with whole blood, component therapy, or both in adult civilian trauma patients: a systematic review and meta-analysis. J Surg Res 2023; 287:193–201.

Systematic review and meta-analysis showing a mortality benefit by combining WB with component therapy vs. component alone.

44. ▪ El-Menyar A, Ahmed K, Hakim S, *et al.* Efficacy and safety of the second in-hospital dose of tranexamic acid after receiving the prehospital dose: double-blind randomized controlled clinical trial in a level 1 trauma center. Eur J Trauma Emerg Surg 2022; 48:3089–3099.

Prospective, double-blind, placebo-controlled randomized, clinical trial of a second in-hospital dose of TXA on survival of trauma patients.

45. Wu F, Kozar RA. Fibrinogen protects against barrier dysfunction through maintaining cell surface syndecan-1 in vitro. Shock 2019; 51:740–744.
46. Stanford S, Roy A, Cecil T, *et al.* Differences in coagulation-relevant parameters: comparing cryoprecipitate and a human fibrinogen concentrate. PLoS One 2023; 18:e0290571.
47. Innerhofer N, Treichl B, Rugg C, *et al.* First-line administration of fibrinogen concentrate in the bleeding trauma patient: searching for effective dosages and optimal post-treatment levels limiting massive transfusion-further results of the RETIC study. J Clin Med 2021; 10:3930.
48. Collins PW, Cannings-John R, Bruynseels D, *et al.* Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. Br J Anaesth 2017; 119:411–421.
49. Lv K, Yuan Q, Fu P, *et al.* Impact of fibrinogen level on the prognosis of patients with traumatic brain injury: a single-center analysis of 2570 patients. World J Emerg Surg 2020; 15:54.
50. Coleman JR, Moore EE, Samuels JM, *et al.* Whole blood thrombin generation in severely injured patients requiring massive transfusion. J Am Coll Surg 2021; 232:709–716.
51. Erdoes G, Koster A, Ortmann E, *et al.* A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and noncardiac surgical patients. Anaesthesia 2021; 76:381–392.
52. Kao TW, Lee YC, Chang HT. Prothrombin complex concentrate for trauma induced coagulopathy: a systematic review and meta-analysis. J Acute Med 2021; 11:81–89.
53. ▪ Go AS, Leong TK, Sung SH, *et al.* Thromboembolism after treatment with 4-factor prothrombin complex concentrate or plasma for warfarin-related bleeding. J Thromb Thrombolysis 2022; 54:470–479.

Multicenter observational study on the 45d risk of thromboembolic events in adults with warfarin-associated major bleeding after treatment with 4F-PCC or plasma.

54. ▪ Bouzat P, Charbit J, Abback PS, *et al.* Efficacy and safety of early administration of 4-factor prothrombin complex concentrate in patients with trauma at risk of massive transfusion: the PROCOAG randomized clinical trial. JAMA 2023; 329:1367–1375.

Double-blind, randomized, placebo-controlled superiority trial in 12 French designated level I trauma centers on the efficacy and safety of 4F-PCC administration in patients at risk of massive transfusion.

55. Bouzat P, Hunt BJ, Juffermans NP. Four-factor prothrombin complex concentrate in trauma patients. Intensive Care Med 2023; 49:1242–1244.
56. Uttaro E, Young MR, Falvey J, *et al.* Use of four-factor prothrombin complex concentrate (4F-PCC) for management of bleeding not associated with therapeutic anticoagulant use. Transfus Apher Sci 2023; 62:103759.
57. Frietsch T, Steinbicker AU, Horn A, *et al.* Safety of intraoperative cell salvage in cancer surgery: an updated meta-analysis of the current literature. Transfus Med Hemother 2022; 49:143–157.
58. Owattanapanich N, Chittawatanarat K, Benyakorn T, Sirikun J. Risks and benefits of hypotensive resuscitation in patients with traumatic hemorrhagic shock: a meta-analysis. Scand J Trauma Resusc Emerg Med 2018; 26:107.
59. Tran A, Yates J, Lau A, *et al.* Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: a systematic review and meta-analysis of randomized controlled trials. J Trauma Acute Care Surg 2018; 84:802–808.
60. Richards JE, Harris T, Dunser MW, *et al.* Vasopressors in trauma: a never event? Anesth Analg 2021; 133:68–79.
61. ▪ Russell RT, Leeper CM, Spinella PC. Damage-control resuscitation in pediatric trauma: what you need to know. J Trauma Acute Care Surg 2023; 95:472–480.

2023 review on modern DCR concepts for pediatric bleeding patients.

62. ▪▪ Russell RT, Esparaz JR, Beckwith MA, *et al.* Pediatric traumatic hemorrhagic shock consensus conference recommendations. J Trauma Acute Care Surg 2023; 94(1S Suppl 1):S2–S10.

2023 clinical recommendations, expert consensus, and good practice statements on pediatric traumatic hemorrhagic shock.

63. Clements TW, Van Gent JM, Lubkin DE, *et al.* The reports of my death are greatly exaggerated: an evaluation of futility cut-points in massive transfusion. J Trauma Acute Care Surg 2023. doi: 10.1097/TA.0000000000003980.
64. Van Gent JM, Clements TW, Lubkin DT, *et al.* Predicting futility in severely injured patients: using arrival lab values and physiology to support evidence-based resource stewardship. J Am Coll Surg 2023; 236:874–880.
65. Moore E, Moore H, Thomas S, *et al.* Serial 'death diamond' TEGs are a bedside indicator of futile resuscitation during massive transfusion – letter-to-the-editor. J Trauma Acute Care Surg 2023; 95:e19–e21.
66. Badami KG, Neal C, Sparrow RL, *et al.* Red blood cell alloantibodies in the context of critical bleeding and massive transfusion. Blood Transfus 2023; 21:390–399.

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